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COMMENTARY

Is mandating elective single embryo transfer ethically justifiable in young women?

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Abstract Compared with natural conception, IVF is an effective form of fertility treatment associated with higher rates of obstetric complications and poorer neonatal outcomes. While some increased risk is intrinsic to the infertile population requiring treatment, the practice of multiple embryo transfer contributes to these complications and outcomes, especially concerning its role in higher order pregnancies. As a result, several jurisdictions (e.g. Sweden, Belgium, Turkey, and Quebec) have legally mandated elective single-embryo transfer (eSET) for young women. We accept that in very high-risk scenarios (e.g. past history of preterm delivery and poor maternal health), double-embryo transfer (DET) should be prohibited due to unacceptably high risks. However, we argue that mandating eSET for all young women can be considered an unacceptable breach of patient autonomy, especially since DET offers certain women financial and social advantages. We also show that mandated eSET is inconsistent with other practices (e.g. ovulation induction and intrauterine insemination—ovulation induction) that can expose women and their offspring to risks associated with multiple pregnancies. While defending the option of DET for certain women, some recommendations are offered regarding IVF practice (e.g. preimplantation genetic screening and better support of IVF and maternity leave) to incentivise patients to choose eSET.

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Introduction

It is well recognised that multiple births, usually the result of the transfer of more than one embryo, pose substantial risks to both mother and infants, and therefore elective single embryo transfer (eSET) should be promoted whenever appropriate. The human female body, with its single uterine cavity and predominance of mono-ovular cycles, has evolved to carry optimally only one baby at a time. Therefore, it can be argued that double-embryo transfer (DET) and its associated risk of twin pregnancy goes against what nature intended, courting obstetric complications. Overall, pre-term delivery rates in IVF conceptions are threefold higher

than in the general population, with low birth weight also being more common (Sunderam et al., 2014). These differences are even more marked in IVF twin pregnancies, with rates of preterm delivery being five times higher than singleton IVF pregnancies, and six times more likely to result in a low birth weight child (Sunderam et al., 2014).

Due to the increased risks associated with IVF twin pregnancies, a number of European countries have now moved to mandated eSET in good prognosis patients (Bissonnette et al., 2011; Maheshwari et al., 2011). For example, Turkey introduced legislation in 2010 which mandates, regardless of embryo quality, that clinicians may transfer a maximum of one embryo in the first one or two cycles in women under the age of 35 (and two embryos

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for subsequent cycles), and a maximum of two embryos in women 35 years or older (Ercan et al., 2014). Sweden and Belgium have similar restrictions mandating eSET in young individuals, with rates of eSET also exceeding 50% in many European countries (Maheshwari et al., 2011; Kupka et al., 2014). In the UK, the National Institute for Clinical Effectiveness (NICE) issued guidance in 2013 that instructs clinicians to use SET for first cycles in women under 37 years of age and for second cycles if a top quality embryo is available (NICE, 2013), while in Australia and New Zealand, the vast majority (85.2%) of embryo transfer cycles for women under 35 years of age are currently conducted as SET (Macaldowie et al., 2014). In the USA, the American Society for Reproductive Medicine (ASRM) guidelines (ASRM, 2013) state that for women under 35 years of age with a favourable prognosis (first cycle of IVF or prior IVF success, good morphology embryos), SET should be offered, while recommending that no more than two embryos should be transferred at a time. However, in the USA the rate of eSET in women under 35 years of age is only 12.2% (Sunderam et al., 2014), despite guidelines suggesting that these patients should be offered eSET (ASRM, 2013). As a result, 46% of infants born from assisted reproduction techniques in the USA were multiple birth deliveries (43% twins, 3% triplets), compared with only 3.4% in the general population (Sunderam et al., 2014).

With such vastly different IVF practices existing around the world, it is timely to ask the question, 'What is the correct approach?' There are two main arguments proposed in favour of a mandated eSET approach. Firstly, DET and a potential multiple pregnancy increases the obstetric risks for women, as well as risks for the children conceived (McLernon et al., 2010; Pinborg et al., 2003; Sazonova et al., 2013). Therefore many commentators argue from a risk minimisation perspective that DET should be avoided at all costs, with the European Society of Human Reproduction and Embryology (ESHRE) Task Force on Ethics and Law even going as far as stating that multiple pregnancies should be reported as IVF complications, not successes (ESHRE Task Force on Ethics and Law, 2003). Secondly, as health care costs related to management of obstetric complications and prematurity are increased in multiple pregnancies, one can also argue from a health economics perspective that eSET should be mandated (Chambers et al., 2014). However, this paper will critically analyse each of these arguments, drawing on four widely endorsed bioethical principles (beneficence, non-maleficence, justice, and respect for patient autonomy) (Beauchamp and Childress, 2001), all commonly used in clinical decision making (Ebbesen and Pedersen, 2007). We argue that in the countries such as the USA, where the majority of IVF costs are borne by the patient, mandated SET is not ethically justifiable.

Beneficence and non-maleficence—Reward is always proportional to risk!

The principle of beneficence requires that doctors' actions benefit patients. However, whenever doctors attempt to produce a medical benefit for patients through treatment, they also place them at risk of harm, since every medical intervention has the potential for adverse outcome. During

medical training, physicians are taught the importance of first avoiding doing harm to patients, or at least minimising any such harm (non-maleficence). The key to being an effective physician, the 'art' of medical practice, is for the doctor to make a balanced judgement of the risks versus benefits of a particular therapy. They are then able to provide a treatment recommendation in light of individual patients' needs and risk profile.

IVF treatment is relatively unique in medical care in that it potentially leads to benefits and risks to both the prospective mother and a third party—the resulting child. Therefore, there is a potential tension between the wishes or interests of one party (the parents) and that of another (the child). It can be argued that a physician has a duty of care to both their current patients (parents) and the future child as several jurisdictions mandate that the doctor must consider the welfare of the child when making decisions regarding fertility treatment (HFEA, 2015; NHMRC, 2007).

The argument in favour of eSET is based on non-maleficence, since it is clear that IVF pregnancies carry higher risk than naturally conceived pregnancies, with this risk being further compounded in multiple pregnancies compared with singletons (ESHRE, 2000; Kjellberg et al., 2006; Sullivan et al., 2012; Sutcliffe and Ludwig, 2007). Furthermore, some may feel that eSET is equally beneficent, since studies from Europe have reported that cumulative pregnancy rates from consecutive eSET are not inferior to those obtained from DET, yet result in a significantly reduced risk of twins (Grady et al., 2012; Lukassen et al., 2005; McLernon et al., 2010; Pandian et al., 2013; Thurin et al., 2004). Does this justify a mandated policy of eSET in all young women?

Firstly, being born prematurely is not necessarily in itself a poor medical outcome. The majority of children born prematurely (between 32 and 37 weeks) ultimately do very well, leading productive adult lives with no major health impediments (Teune et al., 2011). Although such children have an increased risk of short-term and long-term problems, the absolute magnitude of this risk is low (for example, 0.43% of late preterm infants develop cerebral palsy, 0.81% suffer mental retardation, an increase of approximately 0.3% compared with term infants) (Teune et al., 2011). In order to put these risks into perspective, it should be noted that an average individual's life time risk of death as a result of a car accident in the USA is 0.52% (Bandolier, 2015). In everyday life, as well as health care, it is impossible to remove all risk without compromising quality of life or potential benefits.

It is primarily the children born before 32 weeks, and especially those born before 28 weeks, that run significant risk of handicap, chronic health impairment, or even death (Saigal and Doyle, 2008; Serenius et al., 2013). While statistically such very premature deliveries are more common with IVF twins, numerically they are still relatively rare events. The Centers for Disease Control and Prevention (CDC) data on IVF outcomes in the USA report that only 6.7% of IVF twins deliver very prematurely (<32 weeks gestation) (Sunderam et al., 2014). In another study comparing obstetric outcomes resulting from eSET versus DET, the risk of very premature delivery in the DET group was also 6% (McLernon et al., 2010). Overall, a large Danish study reported no significant increase in the rate of cerebral

palsy in IVF twins compared with IVF singletons (3.2% versus 2.5%) (Pinborg et al., 2004). However, it is acknowledged that DET is also associated with an increased risk of stillbirth and neonatal death compared with eSET. For example, an Australian registry study reported that the risk of perinatal mortality following DET was 53% higher than those following SET (a difference of 5.9 deaths per 1000 births), with even singleton births following transfers of fresh DET having 1.3 times increased perinatal mortality compared with those following transfers of fresh SET (Sullivan et al., 2012).

Next, simply showing that there are potential risks from DET is not sufficient to prohibit it. DET has an unusual feature because of the nature of the treatment—two potential children with possible competing health interests. Where two embryos are transferred, it is possible that one of them will be harmed. That embryo is at higher risk than if they had been transferred alone. Later in life, a surviving child might complain that it would have been better (for them) if their parents had only transferred them as a single embryo. However, someone is only harmed if they are left in a worse state than they would otherwise have been. Since a possible alternative for the second embryo is that they will never exist at all in the setting of eSET, it seems that this child, later in life, could well claim to have actually benefited from the DET decision (Wilkinson et al., 2015). The observation that over 600,000 embryos currently remain in cryo-storage in the USA, many long term (Nightlight, 2015), supports the view that many 'second embryos' will never be transferred. Furthermore, while we accept that the moral rights of a 5-day-old embryo are inferior to those of a foetus or child, they are not zero, and therefore still need consideration when assessing the relative merits of a policy of mandated eSET.

Discussions surrounding mandated eSET are often focused on the potential harms of DET, rather than a considered appraisal of its potential benefits. As between 30% and 50% of good-quality blastocysts are genetically abnormal with no potential for normal live birth, even in those women under 35 years of age (Frasasiak et al., 2014), it makes sense that the transfer of two good-quality embryos is more likely to result in the delivery of at least one genetically normal child than the transfer of only one embryo. Transfer of a solitary fresh embryo, followed by a later transfer of a frozen-thawed embryo, could produce comparable cumulative pregnancy rates to a fresh DET, yet lower risk of twins and their associated complications (Grady et al., 2012; Lukassen et al., 2005; McLernon et al., 2010; Pandian et al., 2013; Thurin et al., 2004). However, there are potential costs from such an approach. Firstly, a frozen embryo may not survive the thawing process. Secondly, many couples do not return for a later frozen embryo transfer; either due to psychological distress created by the initial failed fresh transfer, financial impediments or a conscious decision to limit the size of their family to one child after a successful fresh eSET transfer (Brandes et al., 2009; Olivius et al., 2004; Troude et al., 2014). As a result, the 'real world' outcome must mathematically equate with a significant reduction in actual compared with potential cumulative pregnancy rates. Thirdly, the approach of fresh eSET followed by later frozen eSET takes considerably longer (2–3 months) than the DET approach (1 month) for the same cumulative pregnancy outcome—a significant disadvantage

for those women with diminished ovarian reserve and a limited biological window of opportunity for pregnancy. Finally, couples often seek to have two or more children to complete their family. A DET with the delivery of twins may be the best chance for a young woman with low ovarian reserve to complete her family, since there is no guarantee that a frozen embryo will result in a second child, and they may no longer be able to produce any good-quality embryos by the time they have weaned their first child and recommenced IVF treatment.

From a parental perspective, there are also two distinct advantages to DET and the subsequent delivery of twins. Firstly, one pregnancy and period of child rearing is likely to be less disruptive to a woman's career and earning potential than two pregnancies and periods of maternity leave, provided that the twin pregnancy does not result in prolonged medical leave due to complications or mental health issues from the increased stress of caring for twin babies (Vilksa et al., 2009). Furthermore, twins are sometimes perceived to have a special emotional link, forged by 9 months of close proximity in utero and shared passage through life's developmental milestones (Segal, 1999). This special sibling emotional closeness may help explain why as many as one in five couples actually desire twins during IVF treatment (Ryan et al., 2007).

We are not arguing that DET is a superior approach, overall, to sequential SET. Rather, it is not clear that sequential SET is sufficiently more beneficial and less harmful than DET that it should be mandated either by legislation or through restrictive IVF funding arrangements.

Justice

Justice in the context of medical care has two core components—equity and distributive justice. Equity mandates that patients in similar situations should normally have access to the same health care opportunities. In European countries such as Belgium, Denmark, France, and the Netherlands, where the costs of IVF are heavily subsidised by government or private insurance (Maheshwari et al., 2011), it may be ethically justifiable to mandate eSET since the patients are not materially financially disadvantaged if their initial fresh eSET fails and they are required to proceed with a follow-up frozen eSET. However, in countries such as the USA, where the majority of IVF costs are borne by the patients themselves, equity is simply not present as access to fertility treatment is primarily dictated by a patient's financial position, not their medical need. As such, it is arguably unethical to mandate eSET for all couples, irrespective of their financial position and subsequent capacity to continue fertility care beyond their initial fresh embryo transfer.

The second aspect to justice is distributive justice, which emphasises that we have a moral obligation to distribute scarce medical resources fairly among competing medical needs (e.g. fertility care, oncology, infectious disease care, etc.). A distributive justice argument might suggest that eSET should be mandated for all young women because of the increased costs of caring for mothers and babies as a result of complications related to twin delivery (obstetric complications, increased operative delivery, and neonatal

intensive care costs associated with prematurity and long-term health costs associated with caring for a disabled child). A recent UK economic modelling study found that while DET did produce a higher cumulative live birth rate compared with eSET, from a health service perspective, the DET strategy cost an additional US\$42,700 per extra live birth in 32-year-old women and an extra US\$29,000 per extra live birth at 36 years of age (Scotland et al., 2011). However, such modelling fails to account for the additional long-term economic benefit to society derived from the additional children born as a result of DET compared with eSET. Economic modelling suggests that there is on average US\$155,000 net benefit to society for every child born through IVF from lifelong tax contributions, even when direct government costs such as education, health care, and pensions are subtracted (Connolly et al., 2009). Furthermore, this UK economic analysis study made the assumption that all women failing to conceive following eSET would have a frozen embryo available and would return to have that embryo transferred (Scotland et al., 2011). Unfortunately, these assumptions do not reflect actual clinical practice, where embryos of borderline quality can produce healthy babies if transferred fresh (Oron et al., 2014) yet are often not considered of sufficient quality to freeze. Furthermore, financial pressures often cause women not to return for a subsequent frozen embryo transfer. Failure to consider all of these aspects significantly weakens the financially based distributive justice argument against DET. Indeed, these aspects may even favour DET in some circumstances.

Autonomy

Twin pregnancies certainly pose an increased risk to the mother, as well as the child. Almost every obstetric complication is more common in a twin compared with singleton pregnancy, and even life after delivery is more difficult for the parents of twins, with increased risk of postnatal depression, and even divorce (Glazebrook et al., 2004; Pinborg et al., 2003; Vilska et al., 2009). However, autonomy dictates that as adults, we should have the ultimate say on what treatment we receive, within a wide band of reasonable risk, provided that we have been fully informed of those risks and all the associated treatment alternatives (Mill, 2015). The risk/benefit profile of DET seems reasonable, and well within that which patients are normally allowed to choose. Therefore, any increased risks to the mother from DET are not sufficient justification to mandate eSET.

Some commentators would suggest that any increased risk to a child is ethically unacceptable since doctors and parents both have a moral obligation to act in the best interests of the child. However, there are multiple examples where doctors and parents take actions which have the potential to harm a child, yet are still considered to be morally acceptable. For example, we allow parents to decline immunisation of their children, despite the medical evidence clearly showing that the benefits of immunisation far outweigh the risks. Alternatively, we do not usually incarcerate mothers who take drugs or drink excessive amounts of alcohol during pregnancy, to prevent the

potential for harm to their unborn child. Instead, we try to persuade these mothers to minimise risks to their child by reducing or ceasing their potentially harmful behaviour, through education and providing positive health opportunities (e.g. supportive housing where they can live safely and have access to good quality nutrition). Similarly, education of couples regarding the increased risks posed by twin pregnancy is preferable to mandating eSET, since this respects patient autonomy. And as we have argued, the existence of a twin who may not be conceived if sequential SET were employed further complicates doctors' duties to the unborn child in this case.

A balanced approach—eSET is encouraged but not mandated

Two points are clear and not under dispute regarding the optimal number of embryos that may be transferred to a young woman. Firstly, the transfer of three or more embryos is no longer justifiable due to the risk of high-order pregnancy and its associated risks. The current CDC data suggest that in excess of 97% of triplet or higher order assisted reproduction treatment pregnancies will be born prematurely (Sunderam et al., 2014), an unacceptably high risk in today's settings. Secondly, we also accept that the safest approach to creating a healthy baby is through the elective transfer of a single embryo. However, what is currently under debate is whether it is ethically justifiable to mandate eSET, depriving patients of the opportunity to make an informed choice based on their own needs, while also taking away the physician's ability to tailor treatment to best meet their patient's medical and social circumstances. We hope that after reading the preceding discussion, the readership will agree that while eSET may be preferable, mandated eSET is an unethical breach of patient autonomy with modest, or even questionable, overall benefits. Furthermore, if eSET is to be mandated because of concern about the harms or costs of multiple pregnancy, then consistency requires that we also ban ovulation induction or mild ovarian stimulation intrauterine insemination (IUI); both commonly practised fertility treatments with significant risk of multiple pregnancies (Chaabane et al., 2015; ESHRE, 2009; Kupka et al., 2014). Recent European data suggest that 9.3% of IUI cycles will result in twin pregnancies, and 0.5% in triplets (Kupka et al., 2014), whereas North American data report that the risk of multiple pregnancy in ovulation induction alone is increased fourfold compared with natural conception and ninefold when ovulation induction is combined with IUI (Chaabane et al., 2015). The potential costs from abandoning ovulation induction in anovular patients in favour of IVF with mandated eSET would be considerable.

Going forward, we suggest that the optimal path for IVF care is to continue to encourage eSET in young women, supported by the provision of easily understood educational aides (e.g. written patient information sheets and internet-based educational videos) that provide a balanced view of both the benefits and potential downsides of eSET compared with DET. Interestingly, previous work has suggested that an educational DVD is a more effective medium for motivating patients to undertake eSET than a written

brochure containing the same information (Hope and Rombauts, 2010).

Professional societies such as the ASRM and ESHRE should continue to advocate better financial support of IVF care so that couples' decisions on the number of embryos to be transferred are less influenced by financial imperatives. Experience from Belgium has shown that increased government reimbursement of IVF, reducing the personal financial burden on patients, does result in an increase uptake of eSET, with the additional government financial costs being almost completely covered by the associated savings from a reduced need for neonatal care of twins (Ombelet et al., 2005). Similarly, in the USA, a private health insurer has agreed to cover the costs of a frozen cycle eSET if their member undertakes an eSET in the initial fresh transfer, so as to minimise the significant health costs associated with twin pregnancies (Rosenthal, 2013). Finally, the provision of paid maternity leave and the legislative protection of women's jobs while on maternity leave may also help reduce couples' preference for twin deliveries that complete their family in one pregnancy, minimising perceived financial hardship and career disruption.

Furthermore, we believe that guidelines need to be more prescriptive regarding clinical circumstances in which it is never justifiable to perform a multiple embryo transfer, irrespective of a patient's wishes. Gleicher and Barad (2006) have already suggested that in women with a history of previous premature labour, uterine anomalies with a significant risk of preterm labour, or a past history of ruptured uterus, eSET should be mandated, as multiple pregnancy is an unacceptable risk. These contraindications to DET can of course be expanded to include any maternal medical condition that is likely to compromise maternal or foetal health due to the increased physiological burden imposed by a twin pregnancy (e.g. major cardiac or respiratory impairment or advanced maternal age). Furthermore, donor oocyte IVF could also be considered an absolute contraindication to DET as it poses a significantly increased risk of pre-eclampsia and associated complications to mother and child (Le Ray et al., 2012), while also carrying a very high risk of twin pregnancy if the oocytes of a young donor are used. If professional societies such as ASRM or ESHRE were to publish position statements that clearly outline clinical scenarios in which DET is never acceptable, it is unlikely that doctors would act contrary to this type of prescriptive guideline because of fear of litigation and professional censure.

Finally, technological developments such as preimplantation genetic screening (PGS) may ultimately reduce the need for DET by providing optimal pregnancy rates from the elective transfer of a single euploid embryo. A recent meta-analysis of randomised controlled trials using PGS in good prognosis young patients concluded that PGS does result in superior implantation and clinical pregnancy rates compared with the transfer of embryos selected solely on the basis of morphology (Lee et al., 2015). Therefore, we believe that technological approaches such as eSET following PGS are superior to mandated eSET, since they respect patient autonomy, while also optimising pregnancy outcomes. Those countries that currently restrict transfer to eSET, either through law or by prohibiting access to publically funded DET, should revisit their policies and leave this important decision up the patients and their treating physician.

Declaration

KT has a financial interest in fertility care and holds stock in Monash IVF, a publicly listed fertility provider. JS and DW report no financial or commercial conflicts of interest.

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